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Update on infections caused by *Stenotrophomonas maltophilia* with particular attention to resistance mechanisms and therapeutic options

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Stenotrophomonas maltophilia is a Gram-negative, biofilm-forming bacterium. Although generally regarded as an organism of low virulence, *S. maltophilia* is an emerging multi-drug resistant opportunistic pathogen in hospital and community settings, especially among immunocompromised hosts. Risk factors associated with *S. maltophilia* infection include underlying malignancy, cystic fibrosis, corticosteroid or immunosuppressant therapy, the presence of an indwelling central venous catheter and exposure to broad spectrum antibiotics. In this review, we provide a synthesis of information on current global trends in *S. maltophilia* pathogenicity as well as updated information on the molecular mechanisms contributing to its resistance to an array of antimicrobial agents. The prevalence of *S. maltophilia* infection in the general population increased from 0.8–1.4% during 1997–2003 to 1.3–1.68% during 2007–2012. The most important molecular mechanisms contributing to its resistance to antibiotics include β -lactamase production, the expression of *Qnr* genes, and the presence of class 1 integrons and efflux pumps. Trimethoprim/sulfamethoxazole (TMP/SMX) is the antimicrobial drug of choice. Although a few studies have reported increased resistance to TMP/SMX, the majority of studies worldwide show that *S. maltophilia* continues to be highly susceptible. Drugs with historically good susceptibility results include ceftazidime, ticarcillin-clavulanate, and fluoroquinolones; however, a number of studies show an alarming trend in resistance to those agents. Tetracyclines such as tigecycline, minocycline, and doxycycline are also effective agents and consistently display good activity against *S. maltophilia* in various geographic regions and across different time periods. Combination therapies, novel agents, and aerosolized forms of antimicrobial drugs are currently being tested for their ability to treat infections caused by this multi-drug resistant organism.

Keywords: *Stenotrophomonas maltophilia*, prevalence, susceptibility, surveillance, treatment

Stenotrophomonas maltophilia is a Gram-negative, aerobic, glucose non-fermenting, motile bacillus. *S. maltophilia* was first isolated from pleural effusion in 1943 and initially named *Bacterium bookeri*. The organism was reclassified as a member of the genus *Pseudomonas* in 1961, *Xanthomonas* in 1983, and then *Stenotrophomonas* in 1993 (Al-Anazi and Al-Jasser, 2014). It survives on almost any humid surface and has been isolated from a wide variety of aquatic sources, such as suction tubing, nebulizers, endoscopes, hemodialysis dialysate samples, plant rhizosphere, faucets, sink drains, and shower heads (Brooke, 2012). *S. maltophilia* is characterized by its ability to form biofilms on various abiotic and biotic surfaces, including lung cells (de Oliveira-Garcia et al., 2003; Pompilio et al., 2010), and by its resistance to a broad array of antimicrobial agents. The World Health Organization recently classified *S. maltophilia* as one of the leading multidrug resistant organisms (MDROs) in hospital settings (Brooke, 2014).

S. maltophilia is generally regarded as an organism of low virulence and therefore an opportunistic pathogen, especially in immunocompromised hosts. The risk factors associated with acquiring *S. maltophilia* infections are well-known and include underlying malignancy (especially hematologic malignancy), organ transplantation, human immunodeficiency virus (HIV) infection, cystic fibrosis, prolonged hospitalization, intensive care unit (ICU) admission, mechanical ventilation, indwelling catheters (vascular, urinary, biliary), corticosteroid or immunosuppressant therapy, and recent antibiotics treatment (Al-Anazi and Al-Jasser, 2014). These risk factors reflect specific features of *S. maltophilia*, such as its ability to survive on almost any humid surface, its propensity to form biofilm and colonize humid surfaces, and its employment of several mechanisms that confer resistance to a number of antimicrobial agents.

S. maltophilia causes a wide range of infections including respiratory tract infections (RTI), blood stream infections (BSI) and, less commonly, skin and soft tissue infections (SSTI), bone and joint infections, biliary tract infections, urinary tract infections, endophthalmitis, endocarditis, and meningitis (Falagas et al., 2009a; Looney et al., 2009). The correlations between *S. maltophilia* infection and structural abnormalities with or without obstruction or procedural manipulation are well documented. Biliary tract infections caused by obstruction due to hepatobiliary neoplasms (Papadakis et al., 1995; Chang et al., 2014) or post-operative anastomotic strictures of the gastrointestinal tract (Perez et al., 2014) have been reported in patients with biliary *S. maltophilia* sepsis. Pleural infections caused by post-surgical/tube thoracostomy or fistula (broncho-/esophageal-/bilio-) (Lee et al., 2014), post-neurosurgical meningitis (Sood et al., 2013; Lai et al., 2014b), complicated urinary tract infections (Vartivarian et al., 1996), and obstructive lung cancer (Fujita et al., 1996; Vartivarian et al., 2000) have all been reported to create a milieu for *S. maltophilia* infection. In addition, although commonly perceived as nosocomial pathogens, community-acquired infections appear to be on the rise (Falagas et al., 2009a; Chang et al., 2014).

Prevalence

There were few data before 1970 regarding the prevalence or clinical characteristics of *S. maltophilia* (previously *Pseudomonas maltophilia* or *Xanthomonas maltophilia*) because of its rarity and relative clinical insignificance. It was in the 1980s when *S. maltophilia* became more frequently reported as an emerging nosocomial pathogen (Jang et al., 1992; Victor et al., 1994), especially in patients with post-chemotherapy neutropenia (Kerr et al., 1990; Labarca et al., 2000) and in those with indwelling central venous catheters (CVC) (Victor et al., 1994; Lai et al., 2006; Chen et al., 2014). Beginning in the late 1990s worldwide surveillance programs and multi-center studies began to provide more comprehensive information about the pathogenicity of *S. maltophilia*. Of the global surveillance programs, the SENTRY Antimicrobial Surveillance Program initiated in 1997 and the Study for Monitoring Antimicrobial Resistance Trends (SMART) initiated in 2002 are the most well-known (Jean et al., 2015). A number of nationwide and antimicrobial agent-targeted projects were also launched during the late 1990s, including the Canadian Ward Surveillance Study (CANWARD), the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) study, the British Society for Antimicrobial Chemotherapy (BSAC) Resistance Surveillance Project, the Taiwan Surveillance of Antimicrobial Resistance (TSAR) study, and the Tigecycline Evaluation Surveillance Trial (TEST).

Despite the massive scale of these surveillance studies, there are still limited integrated data on the prevalence and susceptibility patterns of *S. maltophilia*. The heterogeneity among the studies stems from the diverse patient demographics, geographic differences, and the ratio of the isolates collected from different sources, making inter-literature comparison difficult. To add to the complexity, there are no worldwide guidelines on susceptibility testing methodology and breakpoints for *S. maltophilia* (Nicodemo et al., 2004; Hombach et al., 2012), which results in different or absence of susceptibility breakpoints for some antibiotics. The lack of universal references for evaluating resistance of *S. maltophilia* to antimicrobial agents leads to confusion and complications when interpreting clinical data.

Table 1 shows the prevalence rates of infection due to *S. maltophilia*, categorized by sources of infection, reported by worldwide and nationwide surveillance projects as well as multi-center studies. Specific patient groups such as the critically ill in intensive care units (ICUs) and the pediatric population are presented separately in **Table 1**. By comparing data gathered by large surveillance studies over time we can estimate longitudinal change in prevalence of *S. maltophilia* infection in the general population. The frequency of occurrence among isolates from all sources ranged from 0.8 to 1.4% in five SENTRY studies during 1997~2003 (Fluit et al., 2001a; Gales et al., 2001a; Sader et al., 2004; Sader and Jones, 2005; Fedler et al., 2006b). During 2007–2012, the CANWARD surveillance study (Zhanel et al., 2011, 2013; Walkty et al., 2014) and the SENTRY antimicrobial surveillance program (Farrell et al., 2010b; Sader et al., 2013) reported prevalence rates ranging from 1.3 to 1.68%. These data indicate that there is an increasing trend in infections due to *S. maltophilia* in the general population.

TABLE 1 | Prevalence of *S. maltophilia* in worldwide surveillance and multicenter studies.

Country ^a	Study ^b	Year	Number of isolates	Prevalence and/or ranking	References
All regions ^c	SENTRY	1997–1999	Total isolates:70067 SM ^d isolates: 842	Among: all pathogens: 1.2%	Gales et al., 2001a
EU	SENTRY	1997–1998	Total/SM isolates in: BSI ^e : 9194/82 RTI: 2052/54 SSTI: 2320/13 UTI: 2138/3	Among: all pathogens: 1.0% BSI: 0.89%, ranking: 19th RTI: 2.63%, ranking: 9th SSTI: 0.56%, ranking: 19th UTI: 0.14%, ranking: 25th	Fluit et al., 2001a
LA	SENTRY	1997–2001	Total isolates: 19547 SM isolates: 166	Among: all pathogens: 0.8%	Sader et al., 2004
All regions	SENTRY	1997–2001	NFGNB ^f isolates: 18569 SM isolates: 1488	Among: NFGNB: 8%	Jones et al., 2003
All regions	SENTRY	1997–2003	Total isolates: 221084 NFGNB ^f isolates: 25305 Uncommon NFGNB ^g : 3509 SM isolates: 2076	Among: all pathogens: 0.94% NFGNB: 8.20% Uncommon NFGNB: 59.16%	Sader and Jones, 2005
All regions	SENTRY	2001–2004	GNB isolates: 54731 NFGNB isolates: 13808 SM isolates: 1256	Among: GNB: 2.29% NFGNB: 9.10%	Gales et al., 2006
Canada	CANWARD	2007–2009	Total isolates: 18538 GNB isolates: 8949 ^h SM isolates: 245	Among: all pathogens: 1.3%, ranking: 17th GNB: 2.7%	Zhanel et al., 2011
AP	SENTRY	2008	Total isolates: 5759 SM isolates: 97	Among: all pathogens: 1.68%	Farrell et al., 2010b
Canada	CANWARD	2008	Total isolates: 5282 SM isolates: 57	Among: all pathogens: 1.1%, ranking: 17th	Zhanel et al., 2010
France	MTC	2008–2009	Total isolates: 46400 Uncommon NFGNB isolates: 158 SM isolates: 61	Among: all pathogens: 0.13% Uncommon NFGNB: 39%	Fihman et al., 2012
Canada	CANWARD	2007–2011	Total isolates: 27123 SM isolates: 378	Among: all pathogens: 1.4%, ranking 16th	Zhanel et al., 2013
All regions	SENTRY	2011	Total isolates: 22005 SM isolates: 362	Among: all pathogens: 1.6%	Sader et al., 2013
Canada	CANWARD	2011–2012	Total isolates: 6593 SM isolates: 104	Among: all pathogens: 1.6%	Walkty et al., 2014
BSI					
USA	SCOPE	1995–1996	NFGNB isolates: 270 SM isolates: 18	Among: NFGNB: 6.7%	Jones et al., 1997
USA, Canada	SENTRY	1997	Total isolates:5058 SM isolates: 40	Among: all pathogens: 0.8%, ranking: 15th In USA: 0.7%, in Canada: 1.1%	Pfaller et al., 1998
NA, LA	SENTRY	1997	Total isolates: 9519 GNB isolates: 4267 SM isolates: 69	Among: all pathogens: 0.7% GNB: 1.6%	Diekema et al., 1999

(Continued)

TABLE 1 | Continued

Country ^a	Study ^b	Year	Number of isolates	Prevalence and/or ranking	References
EU	SENTRY	1997–1998	Total isolates: 9194 SM isolates: 82	Among: all pathogens: 0.89%, ranking: 19th	Fluit et al., 2001a
All regions	SENTRY	1997–1999		Among all pathogens in: AP: 0.9%, Canada: 0.6% EU: 0.9%, LA: 0.8%, USA: 0.7%	Gales et al., 2001a
LA	SENTRY	1997–2000	NA	Among: all pathogens: 0.7% 1997: 0.9%, 1998: 0.8%, 1999: 0.6%, 2000: 0.3%	
LA	SENTRY	1997–2001	Total isolates: 9058 SM isolates: 86	Among: all pathogens: 0.95%	Sader et al., 2004
Worldwide	MTC	2000–2004	All isolates: 26474 SM isolates: 203	Among: all pathogens: 0.8%	Sader et al., 2005b
RTI					
NA	SENTRY	1997	Total isolates: 2757 SM isolates: 99	Among: all pathogens: 3.6%, ranking: 8th In USA: 3.5%, in Canada: 3.7%	Jones et al., 2000
LA	SENTRY	1997	Total isolates: 556 SM isolates: 13	Among: all pathogens: 2.3%, ranking: 8th	Sader et al., 1998
NA	SENTRY	1998	Total isolates: 2773 SM isolates: 114	Among: all pathogens: 4.1%, ranking: 8th In USA: 3.7%, in Canada: 5.9%	Mathai et al., 2001
EU	SENTRY	1997–1998	Total isolates: 2052 SM isolates: 54	Among: all pathogens: 2.63%, ranking: 9th	Fluit et al., 2001a
All regions	SENTRY	1997–1999		Among all pathogens in: AP: 2.8%, Canada: 5.2% EU: 3.2%, LA: 1.8%, USA: 3.3%	Gales et al., 2001a
LA	SENTRY	1997–2000	Total isolates: 2505 SM isolates: 41	Among: all pathogens: 1.6%	Gales et al., 2002
LA	SENTRY	1997–2001	Total isolates: 3346 SM isolates: 60	Among: all pathogens: 1.8%	Sader et al., 2004
NA	SENTRY	2000	SM isolates: 94	Among: all pathogens: 3.5%	Hoban et al., 2003
NA, LA, EU	SENTRY	2004–2008	Isolates from HABP and VABP ⁱ Total cases: 31436	Regional incidence: all regions: 3.1% USA: 3.3%, LA: 2.3%, EU: 3.2%	Jones, 2010
Canada	CANWARD	2008	Total isolates: 1612 SM isolates: 42	Among: all pathogens: 2.6%, ranking: 9th	Zhanel et al., 2010
USA and EU	SENTRY	2009–2012	Total isolates: 12851 GNB isolates: 8201	Among all pathogens in: USA: 4.4%, ranking: 6th EU: 3.2%, ranking: 9th GNB: 6.02%	Sader et al., 2014a
USA and EU	MTC	2012	Total isolates: 2968 SM isolates: 186	Among: all pathogens: 6.3%	Farrell et al., 2014
UTI					
NA	SENTRY	1997	Total isolates: 1698 GNB isolates: 80% SM isolates: 6	Among: all pathogens: 0.35% GNB: 0.44%	Jones et al., 1999b

(Continued)

TABLE 1 | Continued

Country ^a	Study ^b	Year	Number of isolates	Prevalence and/or ranking	References
EU	SENTRY	1997–1998	Total isolates: 138 SM isolates: 3	Among: all pathogens: 0.14%, ranking: 25th	Fluit et al., 2001a
All regions	SENTRY	1997–1999		Among all pathogens in: AP: 0.2%, Canada: 0.0% EU: 0.2%, LA: 0.0%, USA: 0.3%	Gales et al., 2001a
LA	SENTRY	1997–2001	Total isolates: 1961 SM isolates: 0	Among: all pathogens: 0%	Sader et al., 2004
AP region	SMART ^j	2009–2010	Total GNB isolates: 1762	Among all GNB in: China: 1.3%, Thailand: 3.3%	Lu et al., 2012
USA	SMART	2009–2011	Total GNB isolates: 2135 SM isolates: 6	Among: all GNB: 0.28%	Bouchillon et al., 2013
IAI					
China	SMART	2002–2009	Total GNB isolates: 3420 SM isolates: 50	Among: all GNB: 1.5% NFGNB: ranking: 3rd	Yang et al., 2010
AP region	SMART	2003–2010	Total GNB isolates: 20710 NFGNB isolates: 2252 SM isolates: 204	Among: all GNB: 1.0% NFGNB: 9.1%	Liu et al., 2012
Taiwan	SMART	2006–2010	Total GNB isolates: 2417 SM isolates: 28	Among: all GNB: 1.2%	Lee et al., 2012
Africa and middle east	TEST	2007–2012	Total isolates of cSSSI ¹⁴ and IAI from TEST: 1990 and 255 GNB isolates from IAI: 225 SM isolates from IAI: 16	Among: all pathogens in IAI: 6.3% GNB in IAI: 7.3%	Renteria et al., 2014
SSTI					
NA	SENTRY	1997	Total isolates: 1562 SM isolates: 15	Among: all pathogens: 0.96%	Doern et al., 1999
EU	SENTRY	1997–1998	Total isolates: 2320 SM isolates: 13	Among: all pathogens: 0.56%, ranking: 19th	Fluit et al., 2001a
All regions	SENTRY	1997–1999		Among all pathogens in: USA: 1.0%, Canada: 1.1% AP: 0.1%, EU: 0.6%, LA: 0.4%,	Gales et al., 2001a
LA	SENTRY	1997–2001	Total isolates: 1780 SM isolates: 7	Among: all pathogens: 0.39%	Sader et al., 2004
ICU					
EU	SENTRY	1997–1998	Total isolates from ICU: 3981	Among: all pathogens: 1.6%, ranking: 14th BSI: 1.1%, ranking: 15th RTI: 3.0%, ranking: 8th UTI: 0.0%	Fluit et al., 2001b
LA	SENTRY	1997–2001	Total isolates: 19547 SM isolates: 166	Among all pathogens in: ICU: 2.77%	Sader et al., 2004
NA	SENTRY	2001	Total isolates from ICU: 1321 SM isolates: 40 Respiratory source: 89.0%	Among: all pathogens: 3.0%, ranking: 10th	Streit et al., 2004
NA, LA, EU, Asia-Australia area	MTC	2000–2004	Isolates from ICU patients Total isolates: 9093 SM isolates: 131	Among: all pathogens: 1.4%	Sader et al., 2005a

(Continued)

TABLE 1 | Continued

Country ^a	Study ^b	Year	Number of isolates	Prevalence and/or ranking	References
German	SARI	2003–2004	Isolates collected from 39 German ICUs Total isolates: 28266 GNB isolates: 12234	Among all pathogens: Median percentage: 1.7%	Meyer et al., 2006
Canada	CAN-ICU	2005–2006	Isolates from ICU patients Total isolates: 4180 SM isolates: 108	Among: all pathogens: 2.6%	Zhanel et al., 2008
Korea	MTC	2008–2009	Respiratory tract isolates from patient with HABP in ICUs Total isolates: 372 CRGNB isolates: 82 SM isolates: 10	Among: all pathogens: 2.7% CRGNB ^k : 11.6%	Kim et al., 2014
EU	MTC(27) 9 countries	Published in 2011	Respiratory tract isolates from patient with HABP in ICUs Total isolates: 495 SM isolates: 13	Among: all pathogens: 2.6%	Magret et al., 2011
PEDIATRIC POPULATION					
NA	SENTRY	1998–2003	Total isolates: 59826 Total isolates from pediatric patients <7 years: 4641 SM isolates: 166	Among: all pathogens in: all ages: 1.4%, pediatric: 1.2%, both ranking: 10th	Fedler et al., 2006b
NA, LA, EU	SENTRY	2004	Total isolates from pediatric patients ≤18 years: 3537 SM isolates: 53	Among: all pathogens: 1.5%, ranking: 15th all regions combined	Fedler et al., 2006a
COMMUNITY-ACQUIRED					
USA, Canada, LA	SENTRY	1997	BSI SM isolates: 69	CA ^l /N/unknown: 23/28/18 CA: 33.3%	Diekema et al., 1999
UK and Ireland	BSAC	2001–2006	BSI SM isolates: 165	C/N: 31/66 CA: 33%	Livermore et al., 2008
AP region	SMART	2003–2010	IAI SM isolates: 204	CA/N: 26/125 CA: 17.2%	Liu et al., 2012
France	MTC	2008–2009	All sources SM isolates: 61	CA/N: 9/29 CA: 23.7%	Fihman et al., 2012
Taiwan	SMART	2006–2010	IAI SM isolates: 28	CA/N ⁱ : 3/18 CA: 14.3%	Lee et al., 2012

^aNA, North America; LA, Latin America; EU, Europe; USA, the United States of America; UK, United Kingdom; AP, Asia-Pacific.

^bSENTRY, The SENTRY Antimicrobial Surveillance Program; SMART, Study for Monitoring Antimicrobial Resistance Trends; CAN-ICU, The Canadian Intensive Care Unit Surveillance Study; CANWARD, The Canadian Ward Surveillance Study; SARI, Surveillance of Antibiotic Use and Bacterial Resistance in ICUs(German); BSAC, The British Society for Antimicrobial Chemotherapy Resistance Surveillance Project; TEST, Tigecycline Evaluation Surveillance Trial; TIST, Tigecycline In Vitro Surveillance in Taiwan; TSAR, Taiwan Surveillance of Antimicrobial Resistance; SCOPE, Surveillance and Control of Pathogens of Epidemiologic Importance (USA); MTC, multicenter studies.

^cThe SENTRY Antimicrobial Surveillance Program has monitored the predominant pathogens and antimicrobial resistance in 5 geographic regions: Asia-Pacific, Europe, Latin America, Canada, and the United States (Gales et al., 2001a).

^dSM, *Stenotrophomonas maltophilia*.

^eBSI, bloodstream infection; RTI, respiratory tract infection; IAI, intra-abdominal infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection.

^fNFGNB, non-fermentative Gram-negative bacilli

^gUncommon NFGNB, *Acinetobacter* spp. and *Pseudomonas aeruginosa* excluded.

^hOf the 18538 organisms collected, the 20 most common represented 16780 (90.5%) of the isolates and underwent susceptibility testing, which included 8949 (53.3%) Gram-negative bacilli.

ⁱHABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

^jSMART is a global surveillance program that has monitored the in vitro susceptibility patterns of clinical Gram-negative bacilli to antimicrobial agents collected worldwide from intra-abdominal infections since 2002 and urinary tract infections since 2009 (Morrissey et al., 2013).

^kCRGNB, carbapenem-resistant Gram-negative bacteria.

^lC, community-acquired (collected within 48 h of hospitalization); N, nosocomial (collected more than 48 h after hospitalization).

It has been observed in the general population (Gales et al., 2001a) and in ICUs (Fluit et al., 2001b) alike that *S. maltophilia* is most frequently associated with respiratory tract infections (RTIs), followed by bloodstream infections (BSIs), and, rarely, skin and soft tissue infections (SSTIs) and urinary tract infections (UTI) (Gales et al., 2001a). The prevalence of RTIs due to *S. maltophilia* is generally higher than that of other infections caused by that pathogen, but varies widely among countries and continents, ranging from 1.6 to 6.3% during the period 1997–2012 (Sader et al., 1998, 2004, 2014a; Jones et al., 2000; Fluit et al., 2001a; Gales et al., 2001a, 2002; Mathai et al., 2001; Hoban et al., 2003; Jones, 2010; Zhanel et al., 2010; Farrell et al., 2014). The United States has the most consecutive records regarding RTI isolates collected by the SENTRY program. Based on data from four SENTRY studies (Gales et al., 2001a; Hoban et al., 2003; Jones, 2010; Sader et al., 2014a), the prevalence rates increased from 3.3–3.5% during 1997–2004 to 4.4% during 2009–2012. During that 15-year period, *S. maltophilia* went from being the eighth to the sixth most common cause of RTI. In a large study on 2968 RTI isolates collected from 59 medical centers in the USA and 15 centers in European countries in 2012, 6.3% of the pathogens were *S. maltophilia* (Farrell et al., 2014). These observations suggest an increasing frequency of occurrence of respiratory tract infections due to *S. maltophilia*.

S. maltophilia is less frequently isolated from patients with BSIs, UTIs, or SSTIs than from patients with RTIs, with reported isolation rates ranging from 0.7 to 1.1% for BSIs (Jones et al., 1997; Pfaller et al., 1998; Diekema et al., 1999; Fluit et al., 2001a; Gales et al., 2001a; Sader et al., 2004, 2005b), 0–0.3% for UTIs (Pfaller et al., 1998; Jones et al., 1999b; Fluit et al., 2001a; Gales et al., 2001a; Sader et al., 2004, 2005b), and 0.39–0.96% for SSTIs (Diekema et al., 1999; Fluit et al., 2001a; Gales et al., 2001a; Sader et al., 2004). SMART studies have also shown that isolation of *S. maltophilia* from intra-abdominal infections (IAIs) is also fairly uncommon, with rates ranging from 1 to 1.7% (2002–2010) (Guembe et al., 2008; Yang et al., 2010; Lee et al., 2012; Liu et al., 2012). However, data from African and Middle Eastern countries collected as part of the Tigecycline Evaluation Surveillance Trial during 2007–2012 (Renteria et al., 2014) revealed an uncommonly high rate of isolation (6.3%) of *S. maltophilia* from patients with IAIs. In addition, the results from a SMART study surveying UTIs in the Asian-Pacific region during 2009–2010 disclosed higher rates of *S. maltophilia* isolated from patients with UTIs in China (1.3%) and Thailand (3.3%) than in other countries (Lu et al., 2012), although the rates were not as high as those in certain countries in Africa and the Middle East.

Gram-negative Bacilli (GNB) and Non-fermenting Gram-negative Bacilli (NFGNB)

The worldwide rate of isolation of *S. maltophilia* among GNB pathogens ranges from 2.29 to 2.7% according to a SENTRY study (2001–2004) (Gales et al., 2006) and a CANWARD surveillance study (2007–2009) (Zhanel et al., 2011). In the US

state of Texas, however, a study at the M. D. Anderson Cancer Center revealed an increasing trend in the ratio of *S. maltophilia* among GNB isolates obtained from cancer patients during 1986–2002 (from 2% in 1986 to 7% in 2002) (Safdar and Rolston, 2007).

Among NFGNB, *S. maltophilia* has been reported to be the third most commonly isolated pathogen after *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. In a large survey conducted as a part of the SENTRY program, 221,084 GNB isolates were collected worldwide, including 25,305 (11.5%) NFGNB isolates, of which *Acinetobacter* spp. and *P. aeruginosa* accounted for the vast majority (87.7%). The remaining 3509 isolates were deemed unusual NFGNB species. Of them, *S. maltophilia* was the most frequently isolated ($n = 2076$, 59.16%) (Sader and Jones, 2005). A similar finding was reported in a prospective multi-center study involving nine teaching hospitals in France, in which *S. maltophilia* was the most commonly isolated NFGNB among all unusual NFGNB species (39%) (Fihman et al., 2012). Other surveillance studies, namely SCOPE (Jones et al., 1997), SENTRY (Jones et al., 2003; Gales et al., 2006), and SMART (Liu et al., 2012) showed a steady increase in isolation of *S. maltophilia* among all NFGNB pathogens during the period 1995–2010 (6.7% in 1995–1996, 8.0% in 1997–2001, and 9.1% in 2001–2010). These findings show that *S. maltophilia* is not an insignificant pathogen among disease-causing GNB and NFGNB species.

Intensive Care Units, Pediatric Population, and Community-acquired Infections

As expected, the prevalence of infections due to *S. maltophilia* is higher in intensive care units (1.4–3.0%) than in the general population (Fluit et al., 2001b; Sader et al., 2004; Streit et al., 2004; Sader et al., 2005a; Meyer et al., 2006; Zhanel et al., 2008; Magret et al., 2011; Kim et al., 2014).

There is limited information on the worldwide prevalence of *S. maltophilia* infections in the general pediatric population. SENTRY studies conducted during 1998–2003 (Fedler et al., 2006b) and in 2004 (Fedler et al., 2006a) showed that the prevalence of infections due to *S. maltophilia* was 1.2% among children ≤ 7 years and 1.4% among children ≤ 18 years old. The rates are similar to those in the adult population. A comparison of two single-center studies in China and the USA revealed markedly different incidence rates of ventilator-associated pneumonia due to *S. maltophilia* among pediatric patients in ICUs. Ning et al. reported a rate of 20.3% among patients aged 2 months to 16 years in a pediatric ICU in China (Ning et al., 2013) whereas Arthur et al. found that the rate of infection due to *S. maltophilia* among infants aged 0–6 months in a cardiac ICU in the USA was only 0.8% (Arthur et al., 2015).

Several recent studies have shown that *S. maltophilia* is also an emerging opportunistic pathogen in community settings (Falagas et al., 2009a; Chang et al., 2014). Results of a worldwide SENTRY study in 1997 (Diekema et al., 1999) and the British Society for Antimicrobial Chemotherapy Resistance surveillance project conducted during 2001–2006 (Livermore et al., 2008)

showed that 33.3 and 32%, respectively, of *S. maltophilia* isolates were collected within 48 h after admission (defined as community-acquired in these studies) from patients with bloodstream infections. The results from two recent SMART studies revealed that 14.3–17.2% of isolates from patients with community-acquired IAI (also defined by a 48-h time frame within admission) during 2003–2010 were *S. maltophilia* (Lee et al., 2012; Liu et al., 2012). Another recent study on the prevalence of community-acquired *S. maltophilia* BSI in Taiwan, which specifically divided the patients into three categories based on whether they had community-acquired (excluding patients hospitalized within 90 days before admission, cared in a nursing facility, etc.), healthcare-associated or hospital-acquired infections, reported that 17.6% of all community-acquired bloodstream infections were due to *S. maltophilia* (Chang et al., 2014). A similar study in France revealed that 23.7% of all community-acquired BSIs were due to *S. maltophilia* (Fihman et al., 2012). These studies show that community-acquired *S. maltophilia* infections are far less rare than previously thought.

Risk Factors of Mortality

A number of risk factors for death due to *S. maltophilia* infections have been reported. Paez et al. (Paez and Costa, 2008) reviewed the literature from 1985 to 2008 and found that BSI and pneumonia, shock, thrombocytopenia, and Acute Physiological Assessment and Chronic Health Evaluation (APACHE) score >15 are independent risk factors associated with outcome. In addition, underlying hematological malignancy and admission to ICU are independent risk factors for cancer patients. The impact of appropriate antimicrobial treatment and removal of CVC on mortality were concluded to require further clinical studies (Paez and Costa, 2008). The conclusion of the review corresponds to the aforementioned studies. Falagas et al. analyzed 15 articles for attributable mortality of *S. maltophilia* infections. Only four studies provided relevant data regarding inappropriate antibiotic treatment, and three out of the four studies found significantly higher mortality when compared with initial appropriate therapy (Falagas et al., 2009b).

Antimicrobial Susceptibility

There are limited antimicrobial options for infections due to *S. maltophilia* because of its extensive resistance to most antibiotics, including β -lactam antibiotics, cephalosporins, macrolides, aminoglycosides, and carbapenems. Interpretive breakpoints for susceptibility are available only for ticarcillin/clavulanate, ceftazidime, minocycline, levofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), and chloramphenicol (CLSI, 2015). **Table 2** shows the rates of susceptibility of *S. maltophilia* to antimicrobial agents reported in the studies presented in **Table 1**. TMP/SMX is recognized as the drug of choice (Wang et al., 2014a). Resistance rates vary geographically but are generally less than 10% (Chung et al., 2013). However, high and various rates of resistance to TMP/SMX have been reported in patients with cancer

(Vartivarian et al., 1994; Micozzi et al., 2000), cystic fibrosis (Saiman et al., 2002; Cantón et al., 2003; San Gabriel et al., 2004; Valenza et al., 2008), and in several countries, including Taiwan, Japan, Korea, Thailand, Spain, Mexico, Saudi Arabia, Turkey, and Canada (16–78.8%) (Valdezate et al., 2001; del Toro et al., 2002; Lai et al., 2004; Gülmez and Hasçelik, 2005; Memish et al., 2012; Wu et al., 2012; Rattanaumpawan et al., 2013; Rhee et al., 2013; Zhanel et al., 2013; Flores-Treviño et al., 2014; Hotta et al., 2014; Walkty et al., 2014; Wang et al., 2014a). In the present review, global surveillance data for the period 1997–2012 show that *S. maltophilia* continues to be highly susceptible to TMP/SMX (**Table 2**). Over that 15-year period, the susceptibility rates reported in worldwide SENRTY studies (Gales et al., 2001a; Jones et al., 2003; Gales et al., 2006; Sader et al., 2013, 2014a), a BSAC surveillance study (Livermore et al., 2008), and three large-scale multi-national studies (Sader et al., 2005b; Farrell et al., 2010a, 2014) ranged from 90 to 100%.

Ceftazidime and ticarcillin/clavulanate used to be the most effective among β -lactam drugs against *S. maltophilia*. However, recent studies have demonstrated resistance rates of more than 30% and a trend in decreasing susceptibility with ceftazidime (47–75% during 1997–1999 to 30.5–36.8% during 2009–2012) (**Table 2**) (Gales et al., 2001a; Farrell et al., 2010a; Sader et al., 2014b). The same is true for ticarcillin/clavulanate. During 1997–1998, the rates of susceptibility of *S. maltophilia* to that combination ranged from 71–90% but dropped to 27–46.1% during 2003–2008.

New fluoroquinolones exhibit better potency against *S. maltophilia* than ceftazidime or ticarcillin/clavulanate and have become reasonable alternatives. Nonetheless, a comparison of data from worldwide SENTRY studies reveals a decrease in sensitivity of *S. maltophilia* to levofloxacin, from 83.4% during the period 2003–2008 (Farrell et al., 2010a) to 77.3% in 2011 (Sader et al., 2013). Low susceptibility rates ranging from 64–69.6% have also been reported in Canada (Zhanel et al., 2013), China (Yang et al., 2010; Tan et al., 2014), and Korea (Chung et al., 2013). Few multi-center studies have investigated the efficacy of fluoroquinolones against *S. maltophilia* in patients with UTIs. In a SMART study conducted in the Asia-Pacific region, isolates of *S. maltophilia* from patients with UTIs showed exceptionally high rates of resistance to levofloxacin (33.3%) (Lu et al., 2012). Two recent reports showed low MIC₅₀ (minimum inhibitory concentration) values (0.5 mg/L and 0.5 mg/L) and low MIC₉₀ values (8 and 4 mg/L) for moxifloxacin against *S. maltophilia* (Zhanel et al., 2008; Chung et al., 2013), indicating that moxifloxacin could be considered an effective alternative. Data from a number of studies demonstrate that ciprofloxacin has poor activity against *S. maltophilia*, with susceptibility rates averaging lower than 50% (**Table 2**).

Minocycline, doxycycline, and tigecycline have consistently displayed good potency against *S. maltophilia* in studies with various time periods, sources of specimens, and geographic regions (Sader et al., 2005b, 2013, 2014b; Gales et al., 2008; Chen et al., 2012; Wu et al., 2012; Chung et al., 2013). A TSAR surveillance study conducted in Taiwan tested 377 isolates of *S. maltophilia* obtained over a 10-year period (1998–2008) and revealed low MIC₅₀ (0.25 mg/L) and MIC₉₀ values (1 mg/L) for

TABLE 2 | Susceptibility of *S. maltophilia* to various antimicrobial agents in worldwide surveillance and multicenter studies.

Country	Study	Year/ subgroups	TMP/SMX ^d	LEVO ^d	CIP ^d	CAZ ^d	T/C ^d	MCN ^d	TGC ^d	TGCMIC _{50/90}	PB ^d	References
NA, LA	SENTRY	1997		78.0	20.9							Jones et al., 1999a
All regions	SENTRY	1997–1999										Gales et al., 2001a
		AP	92		51	47	71					
		CAN	98		47	60	85					
		EU	90		79	72	86					
		LA	98		57	75	87					
		USA	95		55	67	90					
LA	SENTRY	1997–2001										Sader et al., 2004
		2001	98	98.6	55.7	54.3	45.7				59.2	
		4 years	97.1	88	43.4	57.8	56				NA	
		BSI	95.3	88.4	50	73.3	64					
		RTI	100	90	38.3	46.7	51.7					
All regions	SENTRY	1997–2001	92	86	32	54	86					Jones et al., 2003
All regions	SENTRY	1997–2003	95.3	86.1	30.9	52.9	55.7				67.6	Sader and Jones, 2005
All regions	SENTRY	2001–2004	97	86.9		52.4	47.6				72.4	Gales et al., 2006
NA, LA, EU, AP	MTC	2003–2008										Farrell et al., 2010a
		NA	97.6	82.5		51.0	46.1		94.5 ^a	0.5/2	73.2	
		EU	98.9	83.7		45.2	42.7		95.3		72.6	
		AP	90.8	78.0		32.6	27.0		96.1		33.4	
		LA	95.5	91.3		48.8	36.7		96.5		76.4	
		ALL	96.0	83.4		44.8	39.1		95.5		64.6	
All regions	SENTRY	2011										Sader et al., 2013
		CLSI	94.5	77.3		36.7			92.3 ^a	0.5/2		
		EUCAST	95	NA		NA			79.8			
BSI												
NA, LA	SENTRY	1997	90.9%	81.8	27.3	27.3	90.9					Diekema et al., 1999
NA	SENTRY	1998	73.9	87.0	52.2	65.2	55.7				73.9 ^c	Gales et al., 2001b
All regions	MTC	2000–2004	98.0		29.6	56.9			93.1 ^a	1/2	84.6	Sader et al., 2005b
UK and Ireland	BSAC	2001–2006	100						89 ^b			Livermore et al., 2008

^aTigecycline breakpoints of $\leq 2 \mu\text{g/mL}$ for susceptibility and $\geq 8 \text{ mg/L}$ for resistance were used for comparison purposes only, as defined by the USFDA.

^bSusceptibility to tigecycline at the breakpoint of 1 mg/L used for *Enterobacteriaceae* and *Acinetobacter* spp.

^cResistant strains with colistin and polymyxin B MICs of $\geq 4 \text{ mg/L}$.

^dAntibiotics abbreviations: TMP/SMX, trimethoprim/sulfamethoxazole; LEVO, levofloxacin; CIP, ciprofloxacin; CAZ, ceftazidime; T/C, Ticarcillin/Clavulanate; PB, polymyxin B; TGC, tigecycline; MCN, minocycline.

tigecycline (Wu et al., 2012). Similar results were demonstrated in several large-scale worldwide surveillance studies as well. A recent SENTRY study conducted during 2009–2012 (494 isolates) (Sader et al., 2014a) revealed a susceptibility of 96% and a recent TEST study conducted during 2007–2012 (2245 isolates) (Renteria et al., 2014) demonstrated low MIC₅₀ (0.25 mg/L) and MIC₉₀ (1 mg/L) values.

Molecular Mechanisms in Antimicrobial Resistance

S. maltophilia has several molecular mechanisms contributing to its extensive antimicrobial resistance. The mechanisms are summarized in Table 3. Detailed descriptions of the major mechanisms are elaborated as follows.

TABLE 3 | Molecular mechanisms of antimicrobial resistance in *S. maltophilia*.

Mechanisms	Associated determinants	Related antimicrobial resistance
β-lactamases 1. L1, L2 (chromosomally and plasmid encoded) 2. TEM-2 (on a Tn7-like transposon)	<i>ampR</i> -dependent (involving <i>ampR</i> , <i>ampN-ampG</i> operon, <i>ampD_I</i> and <i>mrcA</i>)	β-lactamases
Class 1 integrons and ISCR elements	<i>sul1</i> , <i>sul2</i> , <i>dfxA</i>	TMP/SMX
Multidrug efflux pump	RND family: <i>SmeABC</i> , <i>SmeDEF</i> , <i>SmeGH*</i> , <i>SmelJK</i> , <i>SmeMN*</i> , <i>SmeOP</i> , <i>SmeVWX</i> , and <i>SmeYZ</i> ABC family: <i>SmrA</i> , <i>MacABCsm</i> MFS family: <i>EmrCABsm</i>	Summarized in Table 4
Qnr	<i>Smqnr</i>	Quinolones and tetracycline
Antibiotic-modifying enzymes	AAC(6′)-Iz, APH(3′)-IIc, AAC(6′)-Iak	Aminoglycoside
Lipopolysaccharide (LPS)	SpgM (phosphoglucomutase)	Aminoglycosides, polymyxin B, ticarcillin/clavulanic acid and piperacillin/tazobactam
Mutations of bacterial topoisomerase and gyrase genes		
Reduction in outer membrane permeability		

*not yet characterized.

β-Lactamases

S. maltophilia has two chromosomal-mediated inducible β-lactamases, namely L1 and L2. L1 is a molecular class B Zn²⁺-dependent metallo-β-lactamase and L2 is a molecular class A clavulanic acid-sensitive cephalosporinase. The L1 and L2 β-lactamases are simultaneously regulated by AmpR, a transcriptional regulator in the L2 upstream region (Okazaki and Avison, 2008). The *ampR-L2* module is homologous to the *ampR-ampC* systems, which are widely distributed in some members of the family *Enterobacteriaceae* and in *P. aeruginosa* (Lodge et al., 1990). The regulation of chromosomal *ampR-ampC* systems has been well studied in *Citrobacter freundii*, where the AmpC β-lactamase induction is linked to peptidoglycan recycling and involves several regulatory genes, such as *ampR*, *ampG*, and *ampD* (Lindberg et al., 1985). A similar induction mechanism was proposed for the *ampR-ampC* and the *ampR-L2* modules (Okazaki and Avison, 2008). But unlike *P. aeruginosa*, the permease system in *S. maltophilia* requires an intact *ampN-ampG* operon for the induction of β-lactamase (Huang et al., 2010). Two *ampD* homologs, *ampD_I* and *ampD_{II}*, were found in *S. maltophilia*, but only *ampD_I* appears to be relevant to the regulation of β-lactamase (Yang et al., 2009).

Penicillin-binding proteins (PBPs) participate in peptidoglycan biosynthesis and the inactivation of PBP4 in *P. aeruginosa* has been shown to confer AmpC overexpression and β-lactam resistance (Moya et al., 2009). The inactivation of a putative PBP1a gene, *mrcA*, recently was found to cause basal-level L1/L2 β-lactamase hyperproduction in *S. maltophilia* KJ. The inactivation of *mrcA* only affects basal L1/L2 production β-lactamase, which is *ampR*- and *ampN-ampG*-dependent, and does not augment their induction (Lin et al., 2011). The universality of disruption of *ampD_I* or *mrcA*

in β-lactamase-hyperproducing *S. maltophilia* mutants and clinical isolates has been proved by the existence of wild-type *ampD_I* and *mrcA* genes. The result implicates mutation of at least one additional gene in this phenotype (Talfan et al., 2013).

Efflux Pumps

Efflux pumps in microorganisms mediate the extrusion of drugs and are classified into five families, namely the resistance-nodulation-cell-division (RND) family, the major facilitator superfamily (MFS), the small multidrug resistance (SMR) family, the ATP binding cassette (ABC) family, and the multidrug and toxic compound extrusion (MATE) family (Putman et al., 2000). Two ABC-type (*SmrA*, *MacABCsm*), one MFS-type (*EmrCABsm*), a fusaric acid extrusion efflux pump (*FuaABC*), and six out of the eight postulated RND-type efflux systems have been characterized in *S. maltophilia* (Alonso and Martinez, 2000; Li et al., 2002; Crossman et al., 2008; Al-Hamad et al., 2009; Chen et al., 2011; Hu et al., 2012; Gould et al., 2013; Huang et al., 2013a; Lin et al., 2014a,b). The six characterized RND-type efflux pumps in the *S. maltophilia* genome are *SmeABC*, *SmeEF*, *SmeIJK*, *SmeOP*, *SmeVWX*, and *SmeYZ* (including *SmeGH* and *SmeMN*). **Table 4** provides a summary of antimicrobial resistance associated with the abovementioned efflux pumps.

SmeABC

The overexpression of *smeABC* genes confers resistance to aminoglycosides, β-lactams, and fluoroquinolones. *SmeC* was identified to function independently of *SmeAB*, while deletions in *smeC* but not *smeB* compromised the antimicrobial resistance (Li et al., 2002).

TABLE 4 | Genetic determinants of efflux pumps.

Efflux pumps	Associated antibiotic resistance
RND FAMILY	
SmeABC	Quinolones, β -lactams and aminoglycosides
SmeDEF	Quinolones, tetracyclines, macrolides, chloramphenicol, novobiocin and trimethoprim/sulfamethoxazole
SmeIJK	Ciproxin, levofloxacin, tetracycline and minocycline
SmeOP-TolCsm	Trimethoprim/sulfamethoxazole, aminoglycosides, macrolides, doxycycline, chloramphenicol, and nalidixic acid
SmeVWX	Quinolones, chloramphenicol and tetracyclines
SmeYZ	Trimethoprim/sulfamethoxazole and aminoglycosides
ABC FAMILY	
SmrA	Fluoroquinolones and tetracycline
MacABCsm	Aminoglycosides, macrolides and polymyxins
MFS FAMILY	
EmrCABsm	Nalidixic acid and erythromycin
FUSARIC ACID TRIPARTITE EFFLUX PUMP	
FuaABC	fusaric acid

SmeDEF

SmeDEF is a complex formed by an efflux pump located on the inner membrane (SmeE), an outer membrane protein (SmeF) and a periplasmic membrane fusion protein (SmeD). It is involved in resistance to quinolones, tetracyclines, macrolides, chloramphenicol and novobiocin (Alonso and Martinez, 2000). Expression of the *smeDEF* operon is regulated by the SmeT repressor (Hernandez et al., 2009). A recent study showed that the SmeDEF efflux pump is associated with plant root colonization by *S. maltophilia*, and that deletion of the *smeE* gene impairs this function (García-León et al., 2014a).

SmeVWX

The SmeVWX pump, encoded by a five-gene operon (*smeU1*, *smeV*, *smeW*, *smeU2*, and *smeX*), was identified and characterized in a multidrug-resistant mutant of *S. maltophilia* KJ. Overexpression of the SmeVWX pump resulted in increased resistance to chloramphenicol, quinolones, and tetracyclines but increased aminoglycoside susceptibility (Chen et al., 2011).

SmeYZ and SmeJK

The *smeZ*, *smeJ*, and *smeK* genes were identified in *S. maltophilia* K M5, a selected mutant derivative. SmeZ contributes to elevated aminoglycoside MICs. SmeJ and SmeK jointly elevate tetracycline, minocycline, and ciprofloxacin MICs and confer resistance to levofloxacin (Gould et al., 2013). In addition to drug extrusion, the SmeIJK pump has been reported to play a physiologic role in the maintenance of cell membrane integrity (Huang et al., 2014). A recent study further elucidated the physiologic significance of the SmeYZ pump and demonstrated its correlation with virulence-related

functions, including swimming, flagella formation, oxidative stress susceptibility, biofilm formation, and protease secretion (Lin et al., 2015).

SmeOP

A *pcm-tolCsm* operon was recently verified in *S. maltophilia* KJ2. The *tolCsm* gene is involved in the resistance of several antimicrobial agents, including aminoglycosides, macrolides, β -lactams, chloramphenicol, nalidixic acid, doxycycline and TMP/SMX. The deletion of *pcm* was shown to result in decreased expression of *tolCsm*, which compromised the pathogen's resistance to amikacin and gentamicin (Huang et al., 2013b). A very recent study characterized a five-gene cluster efflux pump (*tolCsm-pcm-smeRo-smeO-smeP*) in *S. maltophilia*. The study showed that SmeOP requires TolCsm for efflux pump function and suggested that TolCsm is the cognate outer membrane protein (OMP) for the SmeOP pump. The SmeOP-TolCsm efflux pump was shown to be associated with resistance to nalidixic acid, doxycycline, amikacin, gentamicin, erythromycin, and leucomycin (Lin et al., 2014a).

ABC Family: SmrA and MacABCsm

SmrA, the first ABC-type efflux pump identified in *S. maltophilia*, has been shown to confer resistance to fluoroquinolones and tetracycline (Al-Hamad et al., 2009). The MacABCsm efflux pump in *S. maltophilia* was recently shown to confer intrinsic resistance to antimicrobials (aminoglycosides, macrolides, and polymyxins) and to play an important role in regulating oxidative and envelope stress tolerance and biofilm formation (Lin et al., 2014b).

MFS Family: EmrCABsm

Only one MFS-type efflux pump, EmrCABsm, has been characterized so far. It is involved in the extrusion of hydrophobic compounds, including the antibiotics nalidixic acid and erythromycin (Huang et al., 2013a).

Fusaric Acid Tripartite Efflux Pump

A novel tripartite fusaric acid efflux pump was found in *S. maltophilia*, namely FuaABC, which may constitute a new subfamily of the tripartite efflux pump. The *fuaABC* operon was demonstrated to be induced by fusaric acid and to contribute to fusaric acid resistance when overexpressed (Hu et al., 2012).

Trimethoprim/Sulfamethoxazole (TMP/SMX) Resistance Mechanisms

The *sul1* gene carried by class 1 integrons and the *sul2* gene, which is linked to insertion sequence common region (ISCR) elements, are known to be responsible for resistance to TMP/SMX in *S. maltophilia* (Barbolla et al., 2004; Toleman et al., 2007; Chung et al., 2015). The *dhfrA* gene cassettes, which are located in class 1 integrons and encode for the dihydrofolate reductase enzyme, have also been reported to confer high-level resistance to TMP/SMX (Hu et al., 2011). Moreover, SmeDEF, TolCsm, and SmeYZ efflux pumps have recently been reported to be associated with TMP/SMX resistance (Huang et al., 2013b; Lin et al., 2015; Sánchez and Martínez, 2015).

Quinolones Resistance Mechanisms

Two mechanisms are associated with resistance of *S. maltophilia* to quinolones: efflux pumps and a chromosomally encoded *qnr* gene (*Smqnr*) that protects both gyrase and topoisomerase IV from quinolones (Sanchez et al., 2009). Unlike other bacteria, clinical isolates of quinolone-resistant *S. maltophilia* do not present mutations in topoisomerases (Valdezate et al., 2005). To date, the characterized genetic determinants involving resistance to quinolones are *smeDEF*, *smeIJK*, *smeABC*, *smeVWX*, and *Smqnr* genes, among which *smeDEF* and *Smqnr* are the best-described. *Smqnr* belongs to the *qnr* family. It confers low-level resistance and contributes to intrinsic resistance to quinolones in *S. maltophilia* (Sánchez et al., 2008; Shimizu et al., 2008; Sánchez and Martínez, 2010). García-León et al. further elucidated the interplay between intrinsic and acquired resistance to quinolones in *S. maltophilia*. Their study demonstrated that the capacity to develop mutation-driven antibiotic resistance is highly dependent on the intrinsic resistance. Their findings indicate that the most prevalent cause of acquired quinolone resistance in *S. maltophilia* is the overproduction of multidrug efflux pumps, among which *SmeDEF* efflux pump plays the most important role (García-León et al., 2014b). In addition, a more recent report by García-León et al. confirmed that overexpression of *smeVWX* in clinical isolates of *S. maltophilia* is associated with high-level quinolone resistance (García-León et al., 2015).

Aminoglycosides Resistance Mechanisms

The aminoglycoside-resistant mechanisms in *S. maltophilia* primarily involve aminoglycoside-modifying enzymes and efflux pumps. The reported enzymes to date include AAC(6′)-Iz (an aminoglycoside acetyltransferase) (Li et al., 2003), APH(3′)-IIc (an aminoglycoside phosphotransferase) (Okazaki and Avison, 2007) and a novel AAC(6′)-Iak, which was recently identified in a MDR strain from Nepal (Tada et al., 2014). Efflux pumps including *SmeABC*, *SmeYZ*, *SmeOP-TolCsm*, and *MacABCsm* are associated with resistance as described above.

Antimicrobial Treatment Studies

Trimethoprim/sulfamethoxazole (TMP/SMX) remains the most effective antimicrobial agent against *S. maltophilia*, with an overall susceptibility rate higher than 90% (Falagas et al., 2008). A recent study investigated the efficacy of sulfamethoxazole/trimethoprim, an alternative sulphonamide/trimethoprim combination available in several European countries against non-fermenters (40 *S. maltophilia* included) and found that the activity of the alternative combination was similar to that of TMP/SMX (Livermore et al., 2014). Other common options include ceftazidime, ticarcillin-clavulanate, fluoroquinolones, and tetracyclines such as tigecycline, minocycline, and doxycyclines. As previously mentioned, resistance rates to ceftazidime and ticarcillin-clavulanate are high and rising and are, therefore, unreliable choices. Fluoroquinolones are now popular alternatives because of their less prominent side effects compared to TMP/SMX and their greater potency compared to β -lactams.

Fluoroquinolones

Fluoroquinolones (FQs) are commonly used to treat infections due to *S. maltophilia* (Nicodemo and Paez, 2007). However, their overuse worldwide has resulted in higher resistance rates in many kinds of pathogenic bacteria, including *S. maltophilia* (Chang et al., 2014; Pien et al., 2015).

To evaluate the effectiveness of FQs in this era of high FQ resistance, a retrospective study published in 2014 compared the outcomes of patients with *S. maltophilia* infections treated with TMP/SMX and those of patients treated with FQs monotherapy (Wang et al., 2014b). A total of 38 adults received TMP/SMX and 63 adults received FQs (levofloxacin $n = 48$ and ciprofloxacin $n = 15$). The overall microbiological cure rate was 63% (65% in the TMP/SMX group and 62% in the FQ group), and the overall clinical success rate was 55% (61% in the TMP/SXT group and 52% in the FQ group). The antibiotic regimens were equally effective in both groups. Another retrospective study compared the effectiveness of TMP/SMX ($n = 51$) with that of levofloxacin ($n = 35$) in treating *S. maltophilia* bacteremia and revealed no significant differences in treatment outcome between the two groups, including 30-day mortality, length of hospital day, and antibiotic withdrawal (Cho et al., 2014). However, the rate of adverse events was significantly lower in the levofloxacin group (0%) than in the TMP/SXT group (23.5%, $p = 0.001$).

Several new quinolones have been developed and some of them have recently been approved for clinical application, including nemonoxacin (Huang et al., 2015) and delafloxacin (Bassetti et al., 2015). Oral nemonoxacin, a novel nonfluorinated quinolone antibiotic, has been shown to have good activity against Gram-positive bacilli, such as methicillin-resistant *Staphylococcus aureus* (Huang et al., 2015). However, *in vitro* susceptibility assays on 32 clinical isolates of *S. maltophilia* revealed high MIC₉₀ (32 mg/L) and MIC₅₀ (8 mg/L) values (Lai et al., 2014a). Regarding delafloxacin, a phase II study published in 2009 that compared two doses of delafloxacin to tigecycline in adults with complicated skin and skin structure infections found that only one patient was infected with *S. maltophilia* and was treated successfully with delafloxacin (O’Riordan et al., 2015). More *in vivo* studies are needed to better understand the effectiveness of these new quinolones in treating *S. maltophilia* infections.

Tetracyclines

Tetracyclines such as tigecycline, minocycline, and doxycycline are some of the most active antimicrobial agents against *S. maltophilia* other than TMP/SMX, even in the cystic fibrosis population (Cantón et al., 2003; San Gabriel et al., 2004; Gülmez et al., 2010; Milne and Gould, 2012; Castanheira et al., 2014). The results agree with our aforementioned observation that these antibiotics consistently exhibited good activity against *S. maltophilia* in global surveillance studies (Table 2).

Tigecycline, a derivative of minocycline, has broad-spectrum antimicrobial activity (Stein and Babinchak, 2013) and is an alternative agent against *S. maltophilia* infections. A recent study from Brazil showed that the MIC₅₀ and MIC₉₀ values of tigecycline for *S. maltophilia* isolates, including isolates resistant

to levofloxacin and/or TMP/SMX harboring *sul-1*, *sul-2*, and *qnrMR*, were 1 and 4 µg/ml, respectively (Rizek et al., 2015). However, tigecycline has great bio-distribution after intravenous injection, which leads to lower serum drug levels. So, there are concerns about its efficacy for the treatment of bacteremia due to *S. maltophilia* (Stein and Babinchak, 2013). In a recent study, a high dose of tigecycline was effective at treating *S. maltophilia* bacteremia (Wu and Shao, 2014), although in another study, high-dose tigecycline treatment was associated with significant adverse effects (Falagas et al., 2014). In addition, a 3-year clinical therapeutic study that compared the effectiveness of TMP/SMX and tigecycline in treating nosocomial *S. maltophilia* infections revealed no significant differences in mortality or clinical response rates between the two regimens. Clinical improvement rates on the 14th day were 69.2% in the TMP/SMX group and 68.4% in the tigecycline group ($P = 0.954$) and mortality rates on the 30th day were 30.8% in the TMP/SMX group and 21.1% in the tigecycline group ($P = 0.517$) (Tekce et al., 2012). Therefore, tigecycline might be an alternative for patients who are unable to tolerate TMP/SMX. In addition to monotherapy, a combination regimen with tigecycline might be a better option for severe infections, especially for nosocomial infections (Samonis et al., 2012).

In a recent large collection of resistant organisms from the SENTRY program during 2007–2011 (1706 *S. maltophilia* included), minocycline was shown to be significantly more active than other tetracyclines against *S. maltophilia*. The rate of susceptibility of *S. maltophilia* to minocycline exceeded 97% across all geographic regions, and the potency was 2-fold higher than doxycycline (MIC_{50/90}: 0.5/2 µg/mL) (Castanheira et al., 2014). A study evaluated 53 multidrug resistant isolates of *S. maltophilia*, including 48 that were resistant to levofloxacin and/or TMP/SMX, and found that minocycline exhibited excellent activity against *S. maltophilia*. However, the clinical experience is still anecdotal (Rizek et al., 2015). A patient with pneumonia was reportedly successfully treated with minocycline (Irifune et al., 1994), and the combination of minocycline with TMP and ticarcillin/clavulanate has been suggested to be effective (Vartivarian et al., 1994).

Polymyxins and Fosfomycin

Polymyxins and fosfomycin are being reconsidered as alternatives or “last-resort” options because of the increasing emergence of multidrug-resistant organisms. Unfortunately, interpreting the susceptibility rates of *S. maltophilia* to polymyxins is problematic because of the discordance between different testing methods (Nicodemo et al., 2004; Gülmez et al., 2010; Moskowitz et al., 2010; Betts et al., 2014). A SENTRY surveillance program study conducted during 2001–2004 assessed the antimicrobial activity of polymyxin B among 54731 isolates of GNB and 1256 isolates of *S. maltophilia* and found that 72.4% of the *S. maltophilia* isolates were susceptible to polymyxin B (MIC₅₀ and MIC₉₀ values, 1 and 8 mg/L, respectively) (Gales et al., 2006). Colistin (polymyxin E) appears to have a considerable *in vitro* activity against *S. maltophilia* (83–88%) (Falagas and Kasiakou, 2005). In addition, synergy with rifampin, TMP/SMX, and doxycycline has been shown

(Giamarellos-Bourboulis et al., 2002; Gülmez et al., 2010). Two studies by the SENTRY program in the year 2011 (globally) and during 2009–2012 (USA and Europe) that collected 362 and 494 isolates of *S. maltophilia*, respectively, reported very different rates of susceptibility to colistin (98.5%, Sader et al., 2013 and 38.7–49.7%, Sader et al., 2014a). In a recent study that collected 641 isolates of *S. maltophilia* in a university hospital in Argentina (Rodríguez et al., 2014), Rodríguez et al. showed that colistin resistance increased from 8% in 1996 to 45% in 2013 and found that the increase correlated with a marked increase (11.4-fold) in colistin consumption during the study period. Fosfomycin has been shown in several reports to be an inappropriate treatment option because of its poor activity and high MICs against *S. maltophilia* (Macleod et al., 2009; Khan et al., 2014; Rizek et al., 2015).

Combination Therapy

Owing to the impressive array of antimicrobial resistance mechanisms of *S. maltophilia*, various combinations of antimicrobial agents have been surveyed in order to overcome resistance or to attain synergism (Table 5). Combinations of two or three agents with good susceptibility results such as TMP/SMX, ceftazidime, ticarcillin/clavulanate, and aminoglycosides have demonstrated synergistic effects to different degrees in prior studies. In more recent studies, combinations of TMP/SMX or β-lactam/β-lactam inhibitors with new or old antibiotics such as tigecycline, fluoroquinolones, televancin (Hornsey et al., 2012), rifampin (Betts et al., 2014), and aerosolized colistin have been investigated; they demonstrated various extents of synergism and the ability to maintain effectivity in biofilm. TMP/SMX plus ceftazidime plus levofloxacin has been shown to be effective in treatment of meningitis (Correia et al., 2014) and intrabiliary infusion of colistin plus parenteral fosfomycin with tigecycline was reported to be effective at treating complicated biliary tract infection (Perez et al., 2014). Several combinations of novel agents are currently under investigation, including a β-lactam and dual β-lactamase inhibitor combination (Page et al., 2011) and MD3 (a novel synthetic inhibitor of peptidases) plus colistin (Personne et al., 2014). It is important to mention that *in vitro* synergy attained by combination should be further correlated with clinical outcomes.

Nebulized Antimicrobial Agents

Nebulization of antimicrobials results in high concentrations in the respiratory tract and is associated with low toxicity because this method of delivery results in limited systemic absorption (Table 5). These characteristics are especially important for patients with cystic fibrosis, who are prone to frequent infection and colonization of multidrug resistant pathogens including *S. maltophilia*. Wood et al. reported a case of recurrent ventilator-associated pneumonia successfully treated with aerosolized colistin and doxycycline (Wood et al., 2010). King et al. surveyed the *in vitro* pharmacodynamics of aerosolized levofloxacin and suggested that the high concentrations of levofloxacin achieved in the lung by aerosol delivery may be useful for the treatment of patients with cystic fibrosis (King et al., 2010). When *S.*

TABLE 5 | Combinations of antibiotics that demonstrate synergism and nebulized antimicrobial agents.

Year	Combinations	References
COMBINATIONS		
1974	TMP/SMX + colistin	Nord et al., 1974
1979	TMP/SMX + carbenicillin	Felegie et al., 1979
1980	Gentamicin + carbenicillin + rifampin TMP/SMX + carbenicillin + rifampin	Yu et al., 1980
1983	Gentamicin + carbenicillin + rifampicin TMP/SMX + carbenicillin + rifampicin	Berenbaum et al., 1983
1988	Ciprofloxacin + ceftazidime	Chow et al., 1988
1995	Ticarcillin/clavulanate + TMP/SMX Ticarcillin/clavulanate + ciprofloxacin	Poulos et al., 1995
1998	Levofloxacin + various beta-lactams	Visalli et al., 1998
2001	Ticarcillin/clavulanate + aztreonam	Krueger et al., 2001
2002	Azithromycin + TMP/SMX	Saiman et al., 2002
2009	Tigecycline + amikacin Tigecycline + TMP/SMX	Entenza and Moreillon, 2009
2010	TMP/SMX + ticarcillin/clavulanate TMP/SMX + ceftazidime	Gülmez et al., 2010
2012	Ticarcillin/clavulanate + aztreonam: most synergic combination Ticarcillin/clavulanate + colistin Ticarcillin/clavulanate + levofloxacin	Milne and Gould, 2012
2012	Telavancin + colistin: marked synergy	Hornsey et al., 2012
2013	Tigecycline + colistin: best result	Church et al., 2013
2013 ^a	Ceftazidime + colistin ²⁰⁰ Levofloxacin ¹⁰⁰ + ticarcillin/clavulanate Colistin ²⁰⁰ + TMP/SMX	Wu et al., 2013
2013	TMP/SMX + ticarcillin/clavulanate: most synergistic combination	Chung et al., 2013
2014	Ceftazidime + TMP/SMX Ceftazidime + levofloxacin More effective than the combination of TMP/SMX + levofloxacin	Hu et al., 2014
2014	Colistin + rifampin: reliably bactericidal Colistin + tigecycline	Betts et al., 2014
NOVEL COMBINATIONS		
2011	BAL30376: β -lactam and dual β -lactamase inhibitor combination	Page et al., 2011
2014	MD3 + colistin MD3: a novel synthetic inhibitor of SPases (bacterial type I signal peptidases)	Personne et al., 2014

(Continued)

TABLE 5 | Continued

Year	Combinations	References
NEBULIZED ANTIMICROBIAL AGENTS		
2010	Doxycycline + aerosolized colistin	Wood et al., 2010; Harthan and Heger, 2013
2010	Levofloxacin	King et al., 2010
2015	Tobramycin inhalation powder	Ratjen et al., 2015

TMP/SMX, trimethoprim/sulfamethoxazole.

^aThe Top 3 effective combinations when *S. maltophilia* isolates grown as a biofilm. Colistin and levofloxacin were tested at high concentrations (200 and 100 mg/L, respectively), corresponding to the level achievable in sputum by aerosolization.

maltophilia isolates were grown as a biofilm, the top 3 most effective antibiotic combinations included high-dose levofloxacin or colistin delivered at doses achievable by aerosolization plus a β -lactam or TMP/SMX (Table 5) (Wu et al., 2013). The potentials of other antibiotics to be nebulized to achieve high drug levels in airway have been investigated in order to overcome the high MICs that cannot be conquered when the agents are administered systemically. A device (Podhaler device) that delivers new inhalational tobramycin (tobramycin inhalation powder, TIP) and attains high drug levels to the lung may be able to exceed current high MICs of tobramycin in *S. maltophilia* (Ratjen et al., 2015). Waters suggested a potential role of inhaled aztreonam lysine in the treatment of *S. maltophilia* pulmonary infection because of its resistance to the L1 β -lactamase produced by *S. maltophilia* and the ability to achieve high drug levels in respiratory secretions (approximately 1000-fold higher than the corresponding plasma concentration) (Waters, 2012). The antibacterial activity of a novel inhaled combination of fosfomycin and tobramycin (FTI) was investigated in patients with bronchiectasis. However, FTI demonstrated relatively poor activity against *S. maltophilia* (Macleod et al., 2009).

Conclusions

Worldwide, multi-institutional studies confirm that *S. maltophilia* is an emerging multi-drug resistant opportunistic pathogen in hospital and community settings, especially among immunocompromised hosts. TMP/SMX remains the most effective antimicrobial agent in the general population. Drugs with historically good susceptibility results include ceftazidime, ticarcillin-clavulanate, and fluoroquinolones; however, a number of studies show an alarming trend in resistance to those agents. Tetracyclines such as tigecycline, minocycline, and doxycycline are also effective agents and consistently display good activity against *S. maltophilia* in various geographic regions and across different time periods. Combination therapies, novel agents, and aerosolized forms of antimicrobial drugs are currently being tested for their ability to treat infections caused by this multi-drug resistant organism. In addition, recent advances in molecular methods have identified various new mechanisms contributing to drug resistance, which hopefully will lead to future breakthroughs in the treatment of infections due to *S. maltophilia*.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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